Amendments to the Specification

Please amend the following paragraph at page 5, line 21 through page 6 line 3:

According to the invention, FIBULIN-6 (FIBL-6) was screened because of its resemblance to EFEMP1. The protein sequence of FIBL-6 is similar to that of previously identified hemicentin in Caenorhabditis elegans. (Carpten J D, Genomics 64:1-14, 2000; Vogel B E, Hedgecock E M. Development 128:883-94, 2001; Hubbard T, Nucleic Acids Res 30:38-41, 2002.) FIBL-6 maps to 1q25.3-1q31.1, and extends over 450 kb of genomic DNA ~~(http://www.Ensembl.org/Homo_sapiens/geneview?gene=ENSG00000143341)~~. Pairwise alignment ~~(http://www.nebi.nlm.nih.gov/blast/b12seq/b12.html)~~ of the FIBL-6 mRNA with genomic sequence delineated 107 exons that encode a 5,635 amino acid protein with a calculated molecular weight over 600 kDa. The predicted protein consists of an N-terminal von Willebrand factor type A domain, 44 tandem immunoglobulin modules, 6 thrombospondin type 1 domains, a G2 nidogen domain, 7 calcium binding epidermal growth factor-like (cbEGF) domains, and 1 EGF-like domain (FIG. 2).

Please amend the following paragraph at page 6, lines 4-9:

FIBL-6 was considered to be an excellent candidate for the ARMD1 gene because its encoded protein contains a series of predicted cbEGF domains followed by a single EGF-like domain at its carboxy terminus similar to EFEMP1 ~~(http://smart.embl-heidelberg.de/smart)~~. This final EGF-like domain of EFEMP 1 harbors the mutation associated with Mallatia Leventinese, Stone E M, Nat Genet 22:199-202, 1999, an earlier onset macular dystrophy characterized by drusen similar to those seen with AMD.

Please amend the following paragraph at page 39, line 25 through page 40, line 11:

Two-point linkage between the disease locus and each microsatellite marker locus was tested by the parametric lodscore method using a computer program (MLINK). Frequencies of the disease allele and of the normal alleles were assumed to be 0.001 and 0.999, respectively. Based on the pedigree in which there were 3 generations of affected individuals, and male-to-

male transmission, an autosomal-dominant mode of inheritance was assumed. Family members were placed in 1 of 5 age-related liability classes. Age-dependent penetrances for these classes were set to 0.001 (<50 years), 0.01 (50-54 years), 0.09 (55-64 years), 0.42 (65-74 years), and 0.95 (>75 years). These values were determined from a set of 20 similar families with AMD that the inventors identified and are comparable with the prevalence observations reported in three studies based on approximately 15,000 individuals. Allele frequencies reported by the Centre d'Etudes du Polymorphisme Humain (CEPH), Paris, France ~~(http://www.cephb.fr/cephdh/)~~, were used except for markers D15191, D15202, D15461, D15492, and D15412, which were measured in a set of 92 unrelated individuals. Markers for multipoint linkage analysis, whose order was statistically supported, were identified using genotypes from CEPH pedigrees and the computer programs CRI-MAP and MultiMap. Multipoint linkage analysis was conducted using the VITESSE algorithm.

Please amend the following paragraph at page 40, line 22 through page 42, line 14:

Two monoallelic strains (human-mouse cell hybrids), derived from proband 111-3 of family A, were generated by GMP Genetics, Inc. (Waltham, Mass.). One carried the ARMD1 region corresponding to the disease haplotype and the other, a presumably non-disease sequence. Inclusion of the ARMD1 gene locus in the hybrids was verified in the laboratory by genotyping with six microsatellite markers. Exons were mapped on genomic sequence through a pairwise comparison ~~(http://www.ncbi.nlm.nih.gov/blast/b12seq/b12.html)~~ of XM_053531, the reference sequence for FIBL-6 mRNA, with contigs AL121996, AL13S796, AL133515, AL391824, AL118512, AL135797, and AL133553. Primers were designed to amplify each exon plus an additional 50-100 basepairs of the adjacent introns using the Primer3 software package ~~(http://www-genome.wi.mit.edu/cgi-bin/primer/primer3_www.cgi)~~. Genomic DNA (25 ng) was amplified in 20 μl reactions using FastStart Taq DNA polymerase (Roche Diagnostic Corporation Indianapolis, Ind.) with a balcony PCR protocol, which helped to prevent amplification of homologous mouse DNA. All amplifications included an initial denaturation at 95 °C for 5 minutes, a 30-second denaturation at 95° C, an annealing step, and a 1-minute extension at 72° C. "Balcony" refers to the first 10 cycles, in which annealing was performed at 5° C above the T_m of the primers as determined by Primer3 software. This was followed by a 20

cycle touchdown phase in which the annealing temperature dropped in 0.5° C increments from 5° C above the primer T_m to 5° C below. The final phase consisted of 25 cycles in which annealing occurred at 5° C below primer T_m PCR products were electrophoresed on 2% agarose gels, excised, purified with Microcon-PCR Filter units (Millipore Corporation, Bedford, Mass.), and sequenced at the Veteran's Administration Core Sequencing facility (Portland, Oreg.).

Please amend the following paragraph at page *44, line 22 through page 45, line 7:*

Few variations were identified among the 16,905 nucleotides and 5,635 amino acid residues that encode FIBL-6. All 107 exons were sequenced in DNA from seven individuals, representing 12 unique copies of FIBL-6. In addition to the Gln5345Arg change, only one other alteration from the NCBI reference sequence (XM_05353 1) was detected in the proband (111-3) from family A. This was an insertion of 11 bp between the fifth and sixth bases of exon 31. However, this homozygous insertion was also detected in five additional members of family A, 12 unrelated control subjects, and 3 additional individuals. This insertion improves a presumably unusable acceptor site to a potentially functional one ~~(elmo.ims.u-tokyo.ac.jp/altspl/score.html)~~. Therefore, the insertion may better represent the genomic sequence contained in AL118512. Four synonymous (C5086T, C7600T, C13216T, and C16852G) and seven non-synonymous (Ala1624Val, Met2327Ile, Ile2418Thr, Glu2893Gly, His4084Tyr, Asp5087Val, and Arg5188His) changes were found in addition to the Gln5345Arg variation. The Ile2418Thr change, present in the 57-year old control subject, was further investigated by DHPLC. However, because this change was present in 43 of 348 chromosomes from control subjects, it appears to be a common polymorphism.

Please amend the following paragraph at page 45 lines 8-15:

RT-PCR was used to determine if FIBL-6 is expressed in the retina (FIG. 6). Two previously identified clones (AL833232 & AK027344), corresponding to the 3' end of FIBL-6, lacked exon 104, in which the Gln5345Arg variation occurs. Furthermore, intron 103 has a poor acceptor site compared to the consensus sequence for splicing ~~(elmo.ims.u-tokyo.acjp/altspl/score.html)~~. Therefore, gene-specific primers were designed that bridged or

terminated in exon 104. RT-PCR analysis demonstrated FIBL-6 mRNA in human skin fibroblasts, RPE cells, retina, iris, and choroid. Alternative splicing of exon 104 occurred in FIBL-6 transcripts from all tissues examined (FIG. 6).